In This Issue

Cell

Sequencing Lung Cancer

PAGE 1121 and PAGE 1107

Two studies present whole-exome and whole-genome sequencing of lung cancers, the leading cause of cancer-related mortality worldwide. Govindan et al. perform whole-genome sequencing on non-small cell lung cancers and adjacent normal tissue on tumors from 17 patients, including both smokers and never-smokers. Smokers with lung cancer show a 10-fold increase in the number of point mutations than patients who were never-smokers. Imielinski et al. examined a large cohort of lung adenocarcinomas to identify the genomic "hallmarks" underlying the most common type of lung cancer. Both studies provide newly identified gene fusions as fresh targets to study, and alterations in a number of genes for which targeted drugs are available could lead to rapid improvements in clinical care.

The TF Social Network

PAGE 1274

Using genomic DNaseI footprinting, Neph et al. map transcription factor (TF) regulatory networks that connect 475 transcription factors in 41 diverse human cell types. TF networks are highly cell selective and are driven by distinct cohorts of factors that include many regulators with previously unrecognized roles in cellular identity. Taken together, these networks provide a comprehensive look at the circuitry, dynamics, and organizing principles of human transcription factor regulatory networks.

More Than miRNAs for Microprocessor

PAGE 1147

Microprocessor, a complex between the endonuclease Drosha and DGCR8, functions in miRNA biogenesis. Wagscha et al. now report that Microprocessor directly regulates transcription from the HIV-1 promoter and a subset of cellular genes independently of RNAi. Microprocessor works jointly with two exonucleases to cleave nascent RNA transcripts at an internal site, followed by degradation of the downstream sequences, effectively terminating elongation. Subsequent processing of the HIV upstream cleavage product by Rrp6 generates a small RNA implicated in transcriptional repression at the HIV-1 promoter.

Noncoding RNAs Rally Repressive Histone Marks

PAGE 1170 and PAGE 1158

Noncoding RNAs (ncRNAs) are involved in the establishment of repressive chromatin, but how they affect transcription is not fully understood. Two papers now suggest that ncRNAs establish a local repressive state via cotranscriptional chromatin modification. Van Werven et al. find that transcription of an ncRNA, located within the promoter of a sporulation regulator, prevents sporulation in yeast. Transcription of the ncRNA is associated with an increase in the histone marks that recruit the Set2 histone methyltransferase and the Set3 histone deacetylase complexes, leading to the establishment of a repressive chromatin signature at the region. Kim et al. examine the function of Set3 at a genome-wide level and find that Set3 affects transcription during transition periods as genes are induced or repressed. The promoters of Set3-regulated genes are frequently overlapped by noncoding RNAs. These studies suggest that ncRNAs can regulate transcription by shaping histone methylation marks at target promoters.

RING Bearer Joins DSBs to Ubiquitin

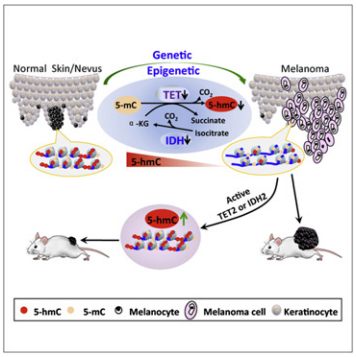
PAGE 1182

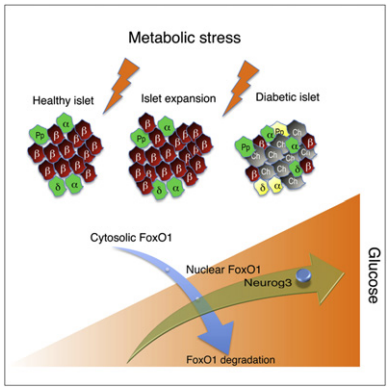
DNA double-strand breaks (DSB) trigger the ubiquitination of histones H2A and H2AX, which is required for DSB repair. Mattiroli et al. uncover K13-15 as the target site for the ubiquitin ligase RNF168 on H2A/H2AX at DSBs. A charged residue in the RING domain of RNF168 controls nucleosomal recognition, which is recruited to DSBs by RNF8. RNF168 monoubiquitinates K13-15 and collaborates with RNF8 to extend K63 chains at this site, enabling the recruitment of downstream effectors for repair.

Methyl Restoration Project Halts Melanoma's Sprawl

PAGE 1135

Abnormal DNA methylation is a key feature of human cancer. Lian et al. find that loss of 5-hydroxymethylcytosine (5-hmC) is an epigenetic hallmark of melanoma and suggest that downregulation of IDH2 and TET enzymes is an underlying mechanism. Rebuilding the 5-hmC landscape by reintroducing TET2/IDH2 suppresses melanoma growth and increases tumor-free survival in animal models of melanoma.





Regressive β Cell Behavior in Diabetes

PAGE 1223

Diabetes is thought to arise through a decrease in pancreatic β cell mass, in part brought about through apoptosis. Talchai and et al. challenge this notion by showing that β cells undergo dedifferentiation during the course of diabetes, effectively regressing to a progenitor-like, multipotent developmental stage. These cells far outnumber apoptotic cells in diabetic mice, raising the possibility that combined cytoprotective and prodifferentiation treatments could restore β cell health and prevent disease progression.

The Ragulator's Gotta Go-To GEF

PAGE 1196

Rag GTPases mediate mTORC1 translocation to the lysosomal surface in response to amino acids, an essential step in mTORC1 activation. The localization of Rags to the lysosome, in turn, depends on the Ragulator complex, but the GEF that activates the Rags is unknown. Bar-Peled et al. now identify HBXIP and C7orf59 as additional components of the Ragulator complex. Surprisingly, the expanded Ragulator shows GEF activity, delineating a lysosome-based signaling system that mediates nutrient sensing by mTORC1.

Single-Cell View of Reprogramming

PAGE 1209

Deciphering the mechanisms of cellular reprogramming has been hindered by the inability to track the few cells in a population that will become induced pluripotent stem cells (iPSCs). Buganim et al. tackle this challenge using single-cell analyses. The authors find that a stochastic phase of gene activation is followed by a late stage in which the pluripotency circuitry is activated hierarchically. In addition, they identify markers that are predictive of successful reprogramming as well as factors that can substitute the classic Yamanaka quartet for iPSC generation.

Right Time, Right Place for T Cell Memory

PAGE 1249

Memory T cells enable rapid responses to repeat infections. Intrinsic differences between memory T cells and naïve T cells have been thought to be important for this special role of memory T cells. However, Sung et al. show that immunological memory for viral infections depends on cytokines and chemokines that guide central memory T cells, but not naïve T cells, to the lymph node periphery, where they can rapidly access viral antigens, suggesting that the kinetics of antigen exposure is a key feature of memory formation.

Neural Stem Cells Bridge the Gap in Spinal Cord Injury

PAGE 1264

Following severe spinal cord injury in rats, Lu et al. show that functional outcomes are improved by the implantation of neural stem cells embedded in a matrix containing a growth factor cocktail. The resulting neurons extend axons over long distances and form reciprocal synaptic connections with neurons from the host.

Mouse Metabolomics

PAGE 1287

Andreux et al. use a large panel of isogenic but diverse strains of BXD type mice to study the genetic control of metabolism. 140 classical phenotypes were generated to allow analysis and dissection of complex metabolic traits and disorders. The authors use this resource to link alkaline phosphatase variants to the bone disease hypophosphatasia.

Node Your Enemy

PAGE 1235

The lymphatic network transports interstitial fluid and antigens to lymph nodes, but this circulatory system is also susceptible to attack from pathogens pursuing systemic spread. Kastenmuller et al. show that a network of diverse lymphoid cells are spatially prepositioned close to sentinel macrophages lining the lymph nodes. In this way, the B, T, and NK cells can rapidly and efficiently receive cytokine signals from pathogen-sensing phagocytes, thus blocking the dissemination of bacteria and viruses that attempt to hijack the lymphatic network.